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ORIGINAL ARTICLE

Reconstructive

Intraoperative Near-infrared Spectroscopy Correlates with Skin Flap Necrosis: A Prospective Cohort Study

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Background: Skin flap necrosis (SFN) is a morbid complication that is disfiguring, leads to acute and chronic wound issues, often requires further surgery, and can delay adjuvant chemotherapy. Although most surgeons rely on the clinical examination, near-infrared (NIR) spectroscopy can extrapolate tissue oxygenation and may serve as an important tool to assess flap perfusion intraoperatively. This cohort study was undertaken to evaluate the capacity of NIR spectroscopy to detect clinically relevant differences in tissue perfusion intraoperatively.

Methods: Patients undergoing oncologic resection of breast cancer, sarcomas, and cutaneous tumors requiring flap reconstruction (local, regional, or free) between January 2018 and January 2019 were analyzed in this study. Clinicians were blinded to device tissue oxygen saturation (S_tO_2) measurements taken intraoperatively after closure and at follow-up appointments in the first 30 days. Measurements were categorized as (1) control areas not affected by the procedure, (2) areas at risk, and (3) areas of necrosis. These areas were retrospectively demarcated by 2 blinded assessors on follow-up images and transposed onto anatomically correlated intraoperative S_tO_2 measurements. Mean S_tO_2 values were compared using a single-sample t test and analysis of variance (ANOVA) to determine differences in oxygenation.

Results: Forty-two patients were enrolled, and 51 images were included in the analysis. Oncologic procedures were predominantly breast (22), postextirpative melanoma (13), and sarcoma (3) reconstructions. Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. Nine patients (20.9%) and 11 surgical sites developed SFN. Mean intraoperative S_tO_2 measurements for control areas, areas at risk, and areas of SFN were 74.9%, 71.1%, and 58.3%, respectively. Relative to control areas, mean intraoperative S_tO_2 measurements were lower by 17.5% ($P = 0.01$) in ultimate areas of SFN and in areas at risk by 5.8% ($P = 0.003$). Relative to areas at risk, mean S_tO_2 measurements from areas of ultimate SFN were lower by 8.3% ($P = 0.04$).

Conclusion: These preliminary data suggest that measuring skin flap tissue oxygenation intraoperatively, with NIR spectroscopy, can differentiate objective variations in perfusion that are associated with clinical outcomes. *(Plast Reconstr Surg Glob Open 2020;8:e2742; doi: 10.1097/GOX.0000000000002742; Published online 22 April 2020.)*

INTRODUCTION

A rapidly evolving area of innovation in the surgical realm, with particular applicability to reconstructive surgery, is the development of adjuvant technology to enhance the clinical assessment of tissue viability. In the context of plastic and reconstructive surgery, understanding the perfusion physiology of tissue provides many advantages for surgical planning, intraoperative decision making, and postoperative surveillance. Most commonly this is achieved by clinical assessment through color, temperature, dermal bleeding, and capillary refill. Unfortunately, even with the most meticulous surgical planning, technique, and clinical assessment, skin flaps

still commonly develop necrosis at rates higher than what may be appreciated in otherwise healthy patients. A recent systematic review by Jeon et al[1] reported a rate of skin flap necrosis (SFN) of 19% following the clinical assessment of mastectomy skin flaps, and other authors report rates up to 30%.[2]

This is a challenging postoperative complication that impacts patients' well-being in numerous ways. Medically, SFN can lead to acute and chronic wound management issues, may delay oncologic therapy, and is associated with psychological morbidity from disfigurement, anxiety, and financial stress.[2] Additionally, this complication is associated with significant cost. A study by Duggal et al[3] in 2014 showed that the cost of unexpected reoperation and associated inpatient hospitalization charges were $16,703 per patient with SFN.

SFN occurs when the blood supply to the skin is inadequate to meet the metabolic demands of the tissue. Thus, a large emphasis is placed intraoperatively and postoperatively on assessing skin flap perfusion. To minimize SFN, most surgeons rely solely on the clinical examination to determine tissue viability. Additional adjuvant tools such as Wood's lamp fluorescein illumination, laser Doppler velocimetry, and indocyanine green angiography (IGA) have been developed to augment the clinical evaluation. The most extensively studied technology to date surrounds the use of IGA. This imaging technique has shown promising data in many observational studies as a reliable tool to reduce postoperative complications and assess tissue viability.[4,5] To date, however, it has not been always feasible to integrate IGA into operative practice due to issues with cost, the need for intravenous contrast, and logistical impracticalities.

Recently, a novel technology that measures tissue oxygen saturation (S_tO_2) through near-infrared (NIR) spectroscopy has been developed. This hand-held device does not require an intravenous injection and instantaneously obtains S_tO_2 measurements by deducing the percentage of oxygenated hemoglobin in the tissue imaged. As a result, it is easily incorporated into the surgical workflow due to its portability and nominal time required to obtain measurements. The lack of an intravenous injection means using this device is noninvasive and is not limited by the recurring costs of disposables.

For NIR spectroscopy to serve as an adjunct to clinical examination alone, it must first be determined if this device has the capacity to detect clinically relevant changes in tissue perfusion intraoperatively. This prospective and blinded study was undertaken to evaluate the capacity of NIR spectroscopy to distinguish clinically relevant differences in intraoperative S_tO_2 measurements predictive of SFN.

METHODS

Patients

Institutional ethics board approval was obtained (HREBA.CC-18-0154) to recruit consecutive patients undergoing oncologic resection and flap reconstruction (local, regional, or free) starting in January 2018. There were no exclusion criteria, apart from patients who did not consent to be part of this study. Written consent was obtained from all patients including consent for photography. All flaps were imaged intraoperatively with the NIR spectroscopy device. The surgeons were blinded to the NIR spectroscopy device measurements taken by an impartial research assistant not involved in the clinical decision making. Intraoperative decisions regarding tissue viability were based solely on the clinical evaluation. NIR spectroscopy S_tO_2 measurements were taken preoperatively, intraoperatively after wound closure, and postoperatively at follow-up clinic visits. Patient demographics, oncologic diagnosis, comorbidities, wound healing risk factors, and operative procedures were recorded. Patients who were followed for 30 days postoperatively to ensure all cases of skin necrosis were included and well demarcated. After discharge, the first follow-up was at 2 weeks if patients did not call to come in sooner. If any concern over necrosis was apparent, then follow-up was scheduled on a weekly basis. Otherwise patients were seen again at 1 month postoperatively to ensure there was no necrosis. During each clinical encounter, NIR spectroscopy measurements were taken with the surgeon who was blinded to the photos. Patients with sufficient imaging data to correlate were included for analysis. In the cases of skin necrosis, wounds were treated by standard wound care principles.

Tissue Hemoglobin Oxygenation (S_tO_2) Imaging

The Kent KD203 SnapshotNIR (Kent Imaging Inc, Calgary, AB, Canada) system was used to measure S_tO_2 intraoperatively, immediate postoperatively, and at follow-up assessments. These measurements required holding the camera parallel to the surgical site at a distance of 30 cm and pressing a button on the device to take a photograph. The resulting oxygenation image covers a field-of-view of 15 × 20 cm. The oxygen saturation measurements reported by the device are weighted toward the smaller arterioles, venules, and capillaries of the imaged vascular bed and gives an indication of the oxygen saturation of hemoglobin in the tissue imaged. The SnapshotNIR system automatically takes a digital color picture at the same time as acquiring the S_tO_2 image. Both images are spatially matched. The color pictures acquired by the device were used to record the visual appearance of the tissue at the time of imaging.

Evaluation and Processing of Color Pictures

Color pictures taken during follow-up examination of the surgical sites were stratified into anatomic zones by 2 blinded clinical evaluators (C.T.-O., W.F.H.). The evaluators identified 3 areas of skin: (1) control areas, (2) areas at risk, and (3) areas of skin necrosis. Control areas were defined as tissue that had been minimally affected by the surgical procedure with similar tissue tone, contour, and quality. Areas at risk were defined as the distal aspects of skin flaps, based on a random pattern of perfusion, that ultimately survive throughout the postoperative surveillance period. Areas of skin necrosis were identified by evaluating images taken at follow-up appointments. Multiple images from a

single patient were excluded unless they were of distinctly different regions of tissue (ie, deep inferior epigastric artery perforator [DIEP] breast and abdomen donor sites).

The follow-up color pictures were then spatially matched to the corresponding intraoperative images after wound closure. Matched images were coregistered using a piecewise linear transformation based on 7–10 pairs of invariant anatomical or other physical landmarks on the tissue. Once spatially registered, the anatomic zones identified on the follow-up color images could be transposed onto intraoperative images taken after wound closure (Fig. 1).

Statistical Analysis

Twenty random pixels, representing 20 distinct S_tO_2 measurements, from each zone identified on the intraoperative S_tO_2 measurements after wound closure were extracted and separated. The mean S_tO_2 values and corresponding 95% confidence intervals were determined for each of the anatomic zones over the study population. Images were excluded if they had an uninterpretable level of artifact affecting S_tO_2 measurements. In this pilot study, patients with deeply pigmented skin were excluded from the analysis. A melanin correction algorithm is available with the device; however, for consistency in the study, it was not used because the algorithm was continuously being improved throughout the study period.

Intraoperative S_tO_2 measurements were analyzed by calculating the difference between both areas at risk and areas of necrosis relative to control areas (Fig. 2). Areas of necrosis were subsequently compared with areas at risk as well (Fig. 3).

Intraoperative S_tO_2 measurements were excluded if the images were inadequate for analysis, such as high burden of artifact from scatter, contour, foreign material, or light glare. Group differences in S_tO_2 from control were considered statistically significant if their 95% confidence intervals did not include 0 (ie, no difference from control).

RESULTS

Forty-two patients and 51 images were included in the analysis (Figs. 4 and 5). Twelve images were unanalyzable due to a high burden of artifact. Average age was 55.7 years (range: 32–87) including 29 women and 13 men. The average weight was 79.1 kg (range: 50–150 kg).

Primary malignancies included 22 breast cancer, 13 melanoma, 3 sarcoma, and 4 other tumors. Patient comorbidities and wound healing risk factors included 12 with a smoking history, 8 with locoregional skin radiation, 6 with hypertension, and 3 with diabetes. Fifteen patients developed postoperative complications which included 11 areas of SFN (in 9 patients), 4 seromas, 3 wound infections, 3 dehiscences, and 1 hematoma. In the 9 patients who developed skin necrosis, there was 1 dehiscence and 1 seroma additionally. Patients with skin necrosis presented on average by postoperative day 10 (range: 4–20). There were no cases of total flap failure, and no patients required reoperation under general anesthetic or implant removal (Tables 1 and 2).

Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. In patients undergoing breast reconstruction, the procedures included 15 alloplastic reconstructions with mastectomy flaps, 3 DIEP flaps, 2 other autologous reconstructions, 1 nipple reconstruction, and 1 revision surgery. Postextirpative melanoma reconstruction was achieved using local rotational flaps and keystone island perforator flaps. For closure of the 3 sarcoma patients, there were 1 pedicled radial forearm flap, 1 pedicled ALT with sartorius flap, and 1 revision ALT flap.

Relative to control areas, mean intraoperative S_tO_2 measurements were lower in areas at risk by 6.9% ($P = 0.003$) and in ultimate areas of necrosis by 17.5% ($P = 0.01$) (Fig. 2). Relative to areas at risk that survived, mean S_tO_2 measurements from areas of ultimate necrosis were lower by 8.3% ($P = 0.04$) (Fig. 3).

DISCUSSION

To assess flap viability, most surgeons rely solely on clinical examination. In isolation, clinical examination has been correlated with a SFN rate of 19% in breast reconstruction and has a low specificity in predicting SFN.[1,6–9] Many clinical adjuncts exist; however, a novel technology has recently been developed that uses NIR spectroscopy to measure S_tO_2.

NIR spectroscopy is a measurement of the interaction between NIR radiation and matter. These interactions lead to reflectance, scattering, or absorption of photons. Reflectance is largely determined by the angle of incidence, whereas absorption and scattering are
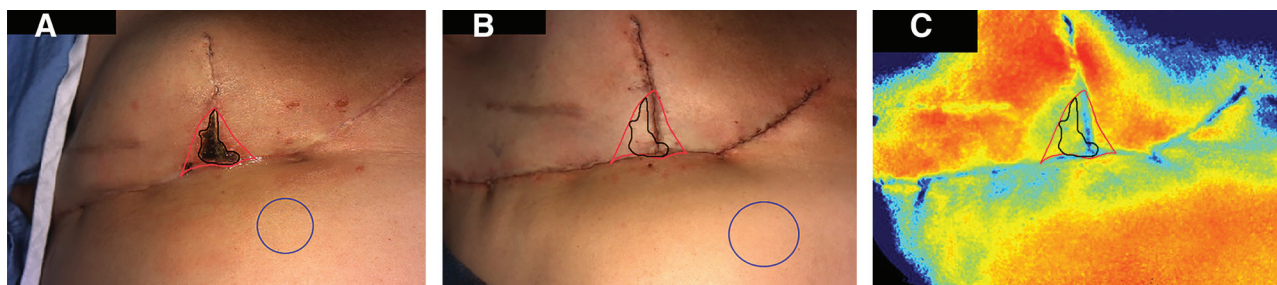

Fig. 1. Pictorial representation of analysis. A, Initially, areas of necrosis were identified at follow-up and the anatomic areas were outlined as necrosis (black), at risk (red) and control (blue). B, Anatomic areas were then transposed on to intraoperative images after closure. C, Mean S_tO_2 values from each zone were calculated using 20 random points from within each area.
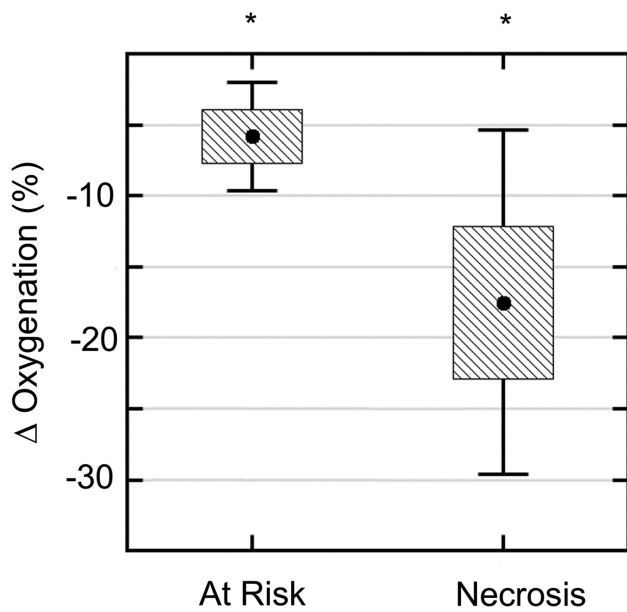
Fig. 2. Mean difference between intraoperative tissue oxygenation of at risk and necrosis zones relative to control zone, with standard error and 95% confidence intervals.
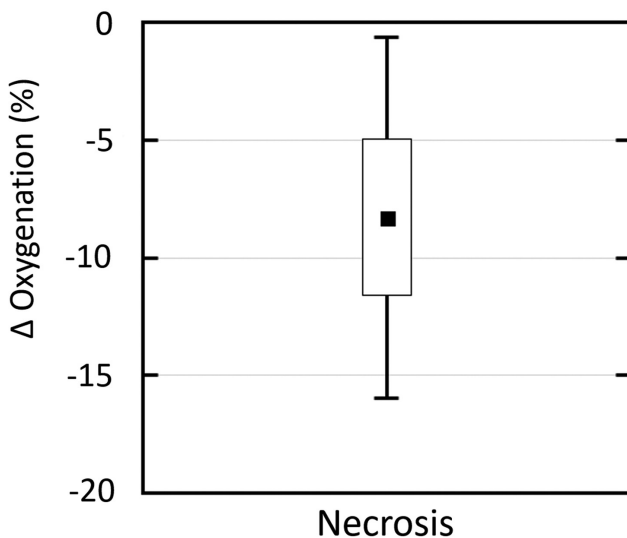

Fig. 3. Mean difference in intraoperative tissue oxygenation between areas at risk and areas of ultimate skin necrosis, with standard error and 95% confidence intervals.

material dependant. Scattering can be minimized with longer wavelengths, such as those in the NIR spectrum, and absorption is directly related to the molecular properties of the material. Above 1,300 nm, water in normally hydrated tissue absorbs photons within a few millimeters. Below 700 nm, there is intense absorption in the visible spectrum, limiting the depth of tissue penetration. NIR radiation between 700 and 1,300 nm optimizes the distance that nonionizing radiation may be transmitted through biologic materials.[9–12] This device emits a spectrum between 600 and 1,000 nm allowing for deeper tissue penetration for more accurate S_tO_2 measurements.

The first description of NIR spectroscopy to continuously and noninvasively monitor oxygen sufficiency was by Jöbsis[9] in 1977. In this article, the author describes the relative transparency of biologic material to NIR radiation and uses NIR spectroscopy to monitor cerebral and myocardial oxygen delivery. Since then it has been reported as a reliable modality for flap monitoring in preclinical and clinical studies; however, a paucity of concerted research efforts has hindered a definitive evidence-based consensus regarding its reliability. Preclinical studies have shown promising results in animal models. Chin et al[12] in 2017 showed that early changes in deoxygenated hemoglobin of random pattern skin flaps, using hyperspectral imaging, may predict the region and extent of flap necrosis in a mouse model. In 2015, Kagaya et al[13] showed that NIR spectroscopy S_tO_2 measurements were indicative of pedicle occlusion in a rat model. When NIR spectroscopy has been translated to the clinical setting, it has been shown as a valuable tool to assess tissue perfusion.[14,15] In 2010, Smit et al[16] reported that NIR spectroscopy had a positive and negative predictive value of 100% for detecting early flap failure and was identified as one of the best monitoring devices. Moubayed et al[17] found that compared with clinical examination, NIR spectroscopy had a salvage rate in compromised flaps of 85% versus 61.5% with a 0% false positive rate. A recent systematic review by Kagaya and Miyamoto[18] in 2018 summarized the current literature surrounding the use of NIR spectroscopy for free flap monitoring. In this study, 15 clinical studies and 8 animal studies were summarized. The use of NIR spectroscopy for S_tO_2 monitoring was able to detect vascular compromise earlier than physical examination and venous Doppler findings with a sensitivity of 99.1% and specificity of 99.9%.[18] NIR spectroscopy has been shown to have a high
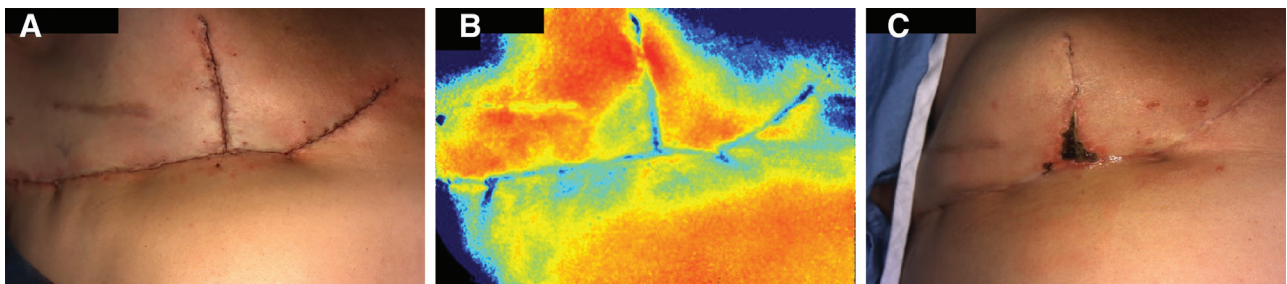

Fig. 4. Female patient undergoing direct-to-implant reconstruction following bilateral skin sparing mastectomies. Imaging of the right breast shows (A) intraoperative color image at closure, (B) associated intraoperative S_tO_2 image at closure, and (C) color image at follow-up showing well-demarcated area of skin necrosis.
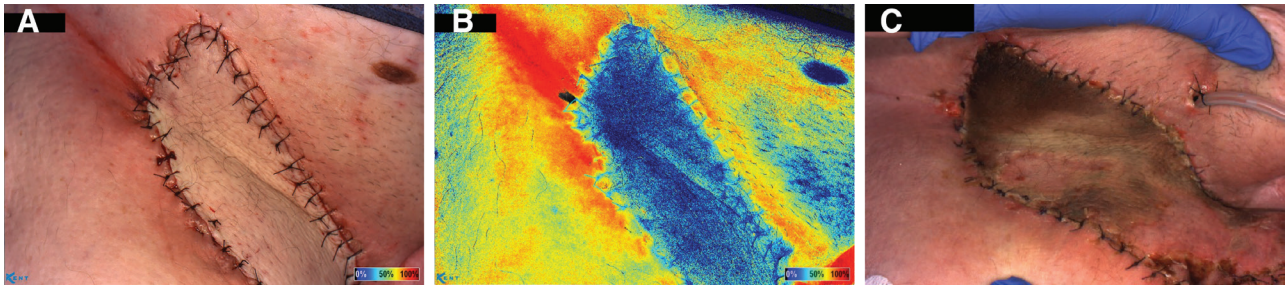
Fig. 5. Male patient undergoing anterolateral thigh and sartorius flap coverage of large defect following resection of a squamous cell carcinoma originating within the right inguinal crease. Imaging shows (A) postoperative color image at closure, (B) associated postoperative S_tO_2 image, and (C) color image at follow-up showing extensive skin flap necrosis.

Table 1. Patient Demographics (N = 42)

Demographics	
Age (y)	55.7
Gender (F)	29 (69%)
Weight (kg)	79.1
Primary malignancy	
Breast cancer	22
Melanoma	13
Sarcoma	3
SCC	1
Rectal cancer	1
Renal cell carcinoma (cutaneous metastasis)	1
Wound healing risk factors	
Smoking	12
Local radiation	8
Hypertension	6
Diabetes	3
Complications	
Skin necrosis	9
Seroma	4
Infection	3
Dehiscence	3
Hematoma	1
Implant removal	0
Flap failure	0
Reoperation	0

SCC, squamous cell carcinoma.

Table 2. Distribution of Complications That Occurred throughout the Surveillance Period

Patient	Skin Necrosis	Infection	Dehiscence	Seroma	Hematoma
A	x		x	x	
B		x		x	x
C		x	x		
D			x		
E				x	
F				x	
G		x			
H	x				
I	x				
J	x				
K	x				
L	x				
M	x				
N	x				
O	x				

degree of accuracy in various clinical situations and shows promise as a clinical adjuvant for detecting flap ischemia. Further research, such as the data presented in this article, is needed to understand the full potential of NIR spectroscopy intraoperatively to justify its routine incorporation.

Laser-assisted indocyanine green (ICG) angiography, such as the SPY *Elite* System (LifeCell Corp, Branchburg, N.J.), has gained attention as a valuable tool in the surgeon's arsenal to evaluate tissue perfusion. Moyer and Losken[19] conducted a study outlining perfusion score parameters that are most predictive of mastectomy SFN. In this study, the authors found that tissue with a perfusion score less than 25% would inevitably result in necrosis, whereas perfusion scores above 45% would unanimously survive. Their study proposed a cutoff of 33% would maximize the resection of nonviable tissue while minimizing the amount of viable tissue that is removed.[19] When looking at clinical outcomes, Mirhaidari et al[4] found that ICG angiography reduced the incidence of full-thickness mastectomy SFN (3.9% versus 10.3%), implant loss (1.9% versus 7.2%), and reoperation (6.3% versus 10.3%) when compared with surgeon assessment alone. Alstrup et al[20] found that ICG angiography was associated with a significant reduction in the rate of major complications in immediate autologous breast reconstruction when compared with clinical assessment (0% versus 23.3%). Hitier et al[21] showed in their pilot study of 20 patients that postoperative complications were detected earlier with ICG angiography than with clinical examination. Sood and Glat[22] found that after the implementation of SPY technology, there were fewer postoperative complications (17.9% versus 36.5%), a significantly lower rate of cases requiring reoperation (0.41 versus 1.21), and that poor flap perfusion could be detected on SPY imaging when clinical assessment alone could not.

One limitation of ICG angiography is the cost associated with this device. This technology itself has an initial cost approaching $300,000 USD and recurring costs from disposables, injection, and operator pay. The upfront cost of the device used in this study is $29,000 USD and does not use any disposables. A cost analysis performed by Kanuri et al[23] found indiscriminate use of ICG angiography in all cases of breast reconstruction would add an additional $1,537.30 per case. However, when used in patients at high risk of mastectomy SFN, namely, smokers, those with a body mass index greater than 30, and those with mastectomy weight greater than 800 g, the use of SPY technology led to a net cost savings per case. This study recommended that, in a healthcare system with finite resources, SPY technology should be reserved for patients who are at high risk of SFN.[23] Other limitations of SPY technology are the logistical issues surrounding the physical size of the machine often disrupting the surgical work

flow and the invasive nature of requiring an intravenous injection.

When contrasting ICG angiography with NIR spectroscopy, some advantages become apparent. Beyond cost, the device evaluated in this study is portable and handheld, thus minimizing interruption in the surgical workflow. It measures S_tO_2 by holding a camera 30 cm, which is indicated to the user through intersecting laser pointers calibrated to intersect at 30 cm from the camera lens. By simply pressing a button that captures an image, the user can obtain an S_tO_2 measurement nearly instantaneously. This offers the capacity to alter clinical decisions based on tissue viability. Options to potentially improve outcomes when poor perfusion is detected may include delaying the flap, excising the distal portion of a skin flap, sending a patient for hyperbaric oxygen, or applying nitroglycerine paste to improve circulation postoperatively.

In this pilot study, we have shown that intraoperative differences in S_tO_2 measurements taken with NIR spectroscopy correlate with the development of skin necrosis in a variety of reconstructive surgeries. With intraoperative decision making guided solely by clinical examination, in a heterogeneous population of flaps, the rate of SFN was 21.4%. This finding is in keeping with a systematic review conducted by Jeon et al[1] who found a mean rate of mastectomy SFN of 19.4% with clinical examination alone. In this study, we found that intraoperative S_tO_2 measurements of areas that eventually develop skin necrosis were lower by 17.5% than control areas ($P = 0.01$). Although these results are promising, we considered it clinically relevant to compare intraoperative S_tO_2 measurements between areas at risk, defined as the distal aspects of the skin flap based on a random perfusion pattern that remained viable, to areas of ultimate necrosis. We found that areas that ultimately develop skin necrosis had intraoperative S_tO_2 measurements that were lower by 6.9% when compared with areas at risk ($P = 0.02$). This study was underpowered to provide accurate measurements of sensitivity and specificity. With these preliminary data, we were able to show a correlation between the use of this device intraoperatively and clinical outcomes. With the full patient cohort, we will be able to robustly define the sensitivity and specificity of this device.

This pilot study is not without its limitations. For patients with darkly pigmented skin, this study did not have a sufficient cohort to examine the utility of this device. A melanin correction is available with the device and will be used in the full patient cohort. This algorithm was continuously being improved by the manufacturer throughout the study which made it impossible to have consistent melanin correction for all patients. Another limitation of this study is the sensitivity of the S_tO_2 measurements to highly contoured surfaces, light glare, and foreign material. For instance, sutures, surgical markings, and hair tend to absorb wavelengths in the NIR spectrum, dampening the reflected wavelengths used to interpret an S_tO_2 measurement. The device best interprets S_tO_2 at an angle of incidence of 90 degrees, maximizing the amount of light reflected back to the device. Highly contoured surfaces reflect light back to the device at different angles, resulting in a higher and uninterpretable burden of artifact. These factors led to the exclusion of 12 images that were impossible to interpret due to artifact. The relatively small sample size made analysis of the sensitivity and specificity of this device limited and not applicable in a clinical context.

To our knowledge, this is the first study evaluating NIR spectroscopy intraoperatively to predict SFN. This pilot study revealed objective differences between viable and critically ischemic tissue and substantiates the application of NIR spectroscopy intraoperatively. A 100-patient experience should yield reliable S_tO_2 parameters to guide intraoperative decisions to preserve viable tissue or resect poorly perfused areas.

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